A RANDOMIZED CONTROLLED TRIAL TO INVESTIGATE DWELL TIME OF SINGLE IMMEDIATE AND ADDITIONAL ADJUVANT INTRAVESICAL CHEMOTHERAPY WITH PIRARUBICIN FOR NON-MUSCLE-INVASIVE BLADDER CANCER FOLLOWING TRANSURETHRAL RESECTION OF BLADDER TUMOR

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Abstract:

〔Introduction〕 Single immediate and additional adjuvant intravesical chemotherapy is the recommended treatment for intermediate-risk non-muscle-invasive bladder cancer (IR NMIBC) patients after transurethral resection of bladder tumor (TURBT). This study aimed to compare two different intravesical retention times of pirarubicin (THP) in IR NMIBC patients from the perspectives of health-related quality of life (HRQoL) and efficacy.

〔Methods〕 One hundred twenty-six patients with bladder tumor were randomized into two study arms prior to TURBT: 30-min and 120-min retention. Patients who were confirmed as IR NMIBC after TURBT received adjuvant intravesical THP instillation. The primary endpoint was change in SF-36 domain scores, International Prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS) from the baseline to after treatment. The secondary endpoints were recurrence-free rate, recurrence-free survival and safety.

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〔Results〕 After TURBT, 59 patients commenced the protocol treatment and 53 patients were assessable as a full analysis set. The changes in scores of SF-36 domains, IPSS and OABSS and recurrence-free survival were not significantly different between the two arms. The most common adverse events (AEs) were urinary tract pain (57.1% vs. 68.0%), urinary frequency (46.4% vs. 24.0%) and hematuria (14.3% vs. 4.0%). More patients in the 120-min group discontinued the treatment due to urinary tract pain. One patient with Grade 3 urinary tract pain and prostate infection was observed only in the 120-min group (1 patient in each AE).

〔Conclusion〕 Thirty-min dwell time for intravesical THP chemotherapy for preventing IR NMIBC recurrence may reduce the risk of adverse events. (Nishinihon J. Urol. **82** : 497-507, 2020)

key words : intermediate-risk non-muscle-invasive bladder cancer, pirarubicin, intravesical chemotherapy

Introduction

Bladder cancer is a malignant tumor with the highest prevalence in the urinary tract in western countries and Japan, and 75% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC)[1]. NMIBC is well known for its unique nature, namely, its frequent recurrence following transurethral resection of bladder tumor (TURBT) and progression into muscle-invasive cancer. For predicting the risk of intravesicular recurrence and progression to muscle-invasive disease, NMIBC can be classified into low-, intermediate- and high-risk groups[2]. For prevention, bladder instillation of chemotherapeutic reagents or Bacillus Calmette-Guerin (BCG) after TURBT is recommended by both EAU and AUA guidelines, depending on risk classification[1) 3)]. In the case of low-risk NMIBC, a single immediate intravesical instillation of chemotherapy after TURBT has been shown to have a beneficial effect on reducing the rate of recurrence[4]. On the other hand, in the case of IR NMIBC, additional adjuvant (or induction) intravesical chemotherapy[5] or BCG immunotherapy[6] in addition to a single immediate instillation is recommended as these have been shown to improve recurrence-free survival. Although BCG seems superior to chemotherapy with regard to prevention of recurrence, the former has a greater risk of adverse events (AEs), such as granulomatous cystitis, hematuria and systemic infection, compared to intravesical chemotherapy[7]. Therefore it is considered that not all cases with NMIBC should be treated with BCG because of the risk of toxicity[8]. Hence, when the risk-to-benefit ratio is considered, intravesical chemotherapy is often employed as a practical choice for preventing recurrence of IR NMIBC in a real clinical setting. However, there is no established protocol in terms of agent selection and dwell time and schedule.

Pirarubicin (THP), a doxorubicin-analogue, is one of the chemotherapeutic options for intravesical instillation against NMIBC. Since several reports have shown that THP exerts faster absorption to bladder cancer than doxorubicin[9) 10)], it is anticipated that the former does not require as long an intravesical retention time as the latter requires, which may result in a better safety profile and an improved quality of life during treatment without compromising treatment efficacy. In fact, a previous report has shown that repeated 30-min dwell time exerts decent THP infiltration in bladder tissue but less toxicity compared to 60-min dwell[11]. However, no prospective study has so far been carried out to identify the optimal dwell time for THP instillation in single immediate or additional adjuvant therapy after TURBT in terms of both prevention of NMIBC recurrence and improved quality of life.

Therefore, we designed this clinical trial to prospectively compare two different dwell times of THP intravesical chemotherapy for both immediate single and additional adjuvant chemotherapy against IR NMIBC. In this study, changes in health-related quality of life (HRQoL) and lower urinary tract symptoms, recurrence-free survival and safety were assessed.

Methods

Study Design

In this multicenter, prospective, randomized controlled study, we recruited patients between 2011 and 2014 at 13 medical centers. The main inclusion criteria were intermediate-risk non-muscle-invasive urothelial carcinoma of the bladder (EORTC recurrence score: 1-9, and progression score: 2) -6)[2] in accordance with the EAU guidelines in 2010. Detailed inclusion and exclusion criteria are shown in **Table 1**. Patients who were diagnosed as having bladder tumor by cystoscopy with the likelihood of IR NMIBC were provisionally registered. Patients were assigned into 2 study arms prior to TURBT by computer-aided randomization procedures using sex, age (65 years of age or older vs. younger than 65), tumor number (4 tumors or more vs. less than 4 tumors), and tumor diameter (3 cm or larger vs. smaller than 3 cm) as stratification factors. One group (the 30-min arm) received an intravesical instillation of 30 mg THP with 30 ml normal saline for 30 min, whereas the other group (the 120-min arm) received the same dose of THP for 120 min. These different dwell times in each of the study arms were applied to both single immediate and additional adjuvant instillations. For the 120-min arm, allowance of dwell time was between 60 and 120 min in case 120 min intravesical retention of THP was not possible due to bladder irritability or pain. After TURBT, all patients received single immediate THP instillation within 24 hr after TURBT. Patients with histologically confirmed IR NMIBC were subject to definitive registration, then proceeded to additional adjuvant intravesical THP instillation. Additional adjuvant instillation was carried out every week for 8 weeks. Allowance of treatment interval was between 4 and 21 days in case weekly instillation was not possible due to AEs including bladder irritability or pain. Follow-up cystoscopy and urine cytology were performed every 3 months for 2 years, then every 6 months during the next year. AEs were continuously and prospectively monitored during the protocol treatment, and recorded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

All patients who were with definitive registration and received at least one protocol-defined additional adjuvant instillation were included in the full analysis set (FAS), and patients who were able to receive at least 5 additional adjuvant instillations were included in the per protocol set (PPS) (**Fig. 1**). The protocol received institutional review board approval in Kumamoto University Graduate School of Medical Sciences, and was conducted according to the Declaration of Helsinki and in line with Good Clinical Practice guidelines. All patients gave their informed

Table 1

Inclusion criteria:
• Histology-proven, completely resected, intermediate-risk non-muscle-invasive urothelial carcinoma of the bladder (EORTC recurrence score: 1-9, and progression score: 2-9),
• The Eastern Cooperative Oncology Group (ECOG) performance status 2 or less.
• Being able to receive regular follow-up cystoscopy for detecting recurrence after TURBT.
Exclusion criteria for provisional registration:
• History of intravesical BCG therapy
• History of additional intravesical adjuvant chemotherapy (single immediate intravesical chemotherapy was permitted)
• Coexisting upper urinary tract cancer
• Other type of active cancers
• Severe heart, liver, renal or hematopoietic disorders, or other conditions that site-investigators considered inappropriate for inclusion in the study.
Exclusion criteria for definitive registration:
• Benign bladder tumor
• Malignant bladder tumor other than urothelial carcinoma
• Low-risk NMIBC (recurrence score: 0, and progression score: 0 or 1)
• High-risk NMIBC (recurrence score: 10 or above, or progression score: 7 or above)
• Muscle-invasive bladder carcinoma.
• Any other conditions which required second TURBT including incomplete resection.
• Carcinoma in situ
• Patients who did not receive single intermediate instillation.

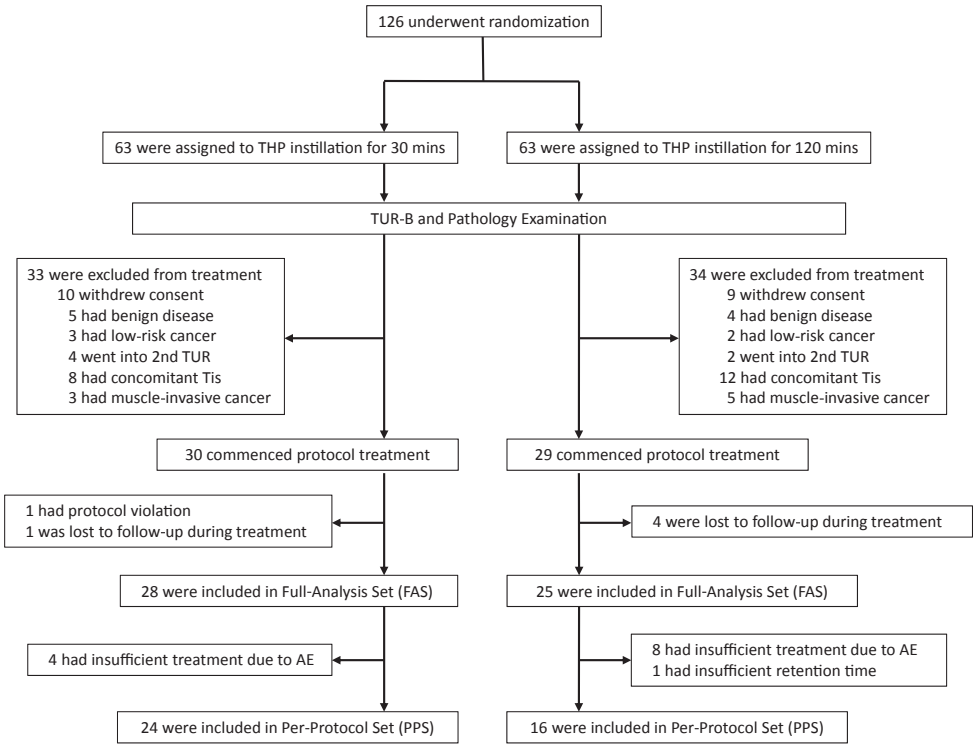


Fig. 1 Patient enrollment and outcomes.

consent by signature. This trial has been registered in the UMIN Clinical Trials Registry (UMIN-CTR, Trial registration: UMIN000006861).

Endpoints

The primary endpoint was the change in HRQoL and lower urinary tract symptoms from the baseline and after the protocol treatment. For the assessment of HRQoL, the Japanese version 2.0 of SF-36 was used[12]. We standardized these domain scores using Japanese population norm-based scoring to give a mean of 50 and a standard deviation of 10[12) 13)]. For the assessment of lower urinary tract symptoms, the International Prostate Symptom Score (IPSS) questionnaire (question 8, QoL due to urinary symptoms, was separately analyzed as IPSS-QoL) and Overactive Bladder Symptom Score (OABSS) were used. In this study, patients were asked to hold the questionnaire book containing SF-36, IPSS and OABSS, and answer the questionnaire by themselves. These measurements were done before TURBT (baseline), at each visit for additional adjuvant intravesical THP instillation and 3 months after completion of the protocol treatment. The secondary endpoints were recurrence-free rate at 1, 2 and 3 years, recurrence-free survival, defined as the time from randomization to the first recurrence, and safety.

Statistical Analysis

Our hypothesis was (1) 30 min is nominally inferior to 120 mins with regard to the non-recurrence rate with a clinically acceptable difference, (2) 30 min is superior to 120 min with regard to HRQoL and safety, and (3) therefore, in total, 30-min dwell time can also be a clinically acceptable option. However, there has been no previous clinical trial reporting either safety or the recurrence-free survival of IR NMIBC by additional adjuvant intravesical chemotherapy by weekly 30 mg THP instillations, which thereby hampered the design of a confirmatory non-inferiority study. Therefore, to select "less harmful" treatment without compromising the efficacy, we calculated the sample number according to the randomized phase II selection design[14] by using the following link for the calculation algorithm (https://www2.ccrb.cuhk.edu.hk/stat/phase2/Randomized.htm). We hypothesized

that the recurrence-free survival rates at 2 years by the 30-min and 120-min instillations were 60% and 70% (considering less than 10% difference in non-recurrence rate at 2 years is clinically acceptable), respectively, and the probability of correctly selecting the better treatment is 90%. Based on this hypothesis, 75 patients were required in each arm if the likelihood of selecting the "better" protocol was 90%. The primary endpoint was supposed to be analysed in ITT subjects. However, since we could collect the questionnaire book with analyzable data from only a very limited number of patients who completed the protocol treatment, only analysis in "incomplete" PPS population was consequently feasible. The secondary endpoints were analyzed in FAS subjects. ANCOVA models were used to estimate the difference in changes of the SF-36 subscales, IPSS, IPSS-QoL and OABSS between the two study arms. The value at the baseline was used as covariate for all measurements. All statistical analysis was performed using EZR ver. 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[15], except for JMP Pro 13.2.1 (SAS Institute, Cary, NC) for ANCOVA analysis. All p values were two-tailed, and $p<0.05$ was taken as statistically significant.

Results

Patients

Between 2011 and 2014, 126 patients underwent randomization. After exclusion of those who did not meet the inclusion criteria (summarized in **Fig. 1**), 30 patients in the 30-min arm and 29 patients in the 120-min arm commenced the protocol treatment. After exclusion of those who had an incomplete record and/or protocol violation, 28 patients in the 30-min arm and 25 patients in the 120-min arm were subject to FAS (**Fig. 1**). Among them, 24 patients in the 30-min arm and 16 patients in the 120-min arm completed the protocol treatment. There was no statistically significant difference in patient demographics between the 2 treatment arms subject to FAS (**Table 2**). The 30-min and 120-min arms received 7.9 and 7.4 THP instillations on average, respectively.

Table 2 Baseline demographics and clinical characteristics.

Characteristics	30 mins (N=28)	120 mins (N=25)	P value*
Age, yr			
Median (range)	70 (36-85)	69 (36-89)	0.857
18-64	12	7	0.390
≥65	16	18	
Sex			
Male	22	19	1
Female	6	6	
ECOG-PS			
0	24	24	0.115
1	4	0	
Urine cytology			
Negative	19	19	0.618
Suspicious	6	3	
Positive	2	1	
N.A.	1	2	
Primary or Recurrence			
Primary	24	22	1
Recurrence	4	3	
Tumor diameter			
<3 cm	26	23	1
≥3 cm	2	2	
Tumor number			
<4	24	24	0.355
≥4	4	1	
Tumor morphology			
Papillary	23	23	0.115
Non-papillary	4	0	
N.A.	1	2	
With stalk	22	16	0.508
Sessile	5	7	
N.A.	1	2	
Tumor pathology			
Grade			
G1	5	5	0.732
G2	23	19	
G3	0	1	
pT stage			
pTa	24	23	0.672
pT1	4	2	

*Mann-Whitney U test

Health-Related Quality of Life and Lower Urinary Tract Symptoms

Questionnaire results regarding SF-36 domains, IPSS total score (IPSS-T), IPSS voiding symptom (IPSS-V), IPSS storage symptom (IPSS-S), IPSS-QoL and OABSS were obtained from 12 and 10 patients in the 30-min and the 120-min arms, respectively. The medians and interquartile ranges of those scores at the baseline and after the protocol treatment are shown in **Fig. 2 A** (SF-36 domains) and **B** (lower urinary symptoms scores). When comparing the two study arms, changes from the baseline were not statistically significant in

any SF-36 domains (p value: 0.2181 for PF, 0.1700 for RP, 0.6042 for BP, 0.1693 for GH, 0.2544 for VT, 0.0989 for SF, 0.0631 for RE and 0.3164 for MH). This was also the case with lower urinary symptom scores (p value: 0.2308 for IPSS-T, 0.2489 for IPSS-V, 0.1488 for IPSS-S, 0.4446 for IPSS-QoL and 0.6753 for OABSS).

Efficacy

At the time of data cut-off, an event of disease recurrence had occurred in 5 patients in the 30-min group, and 6 patients in the 120-min group. The recurrence-free survival rates in FAS were 92.9% (95% CI: 74.3-98.2) vs. 83.3% (95% CI: 61.3-93.4) at 1 year, 88.8% (95% CI: 69.1-96.3) vs. 78.9% (95% CI: 56.6-

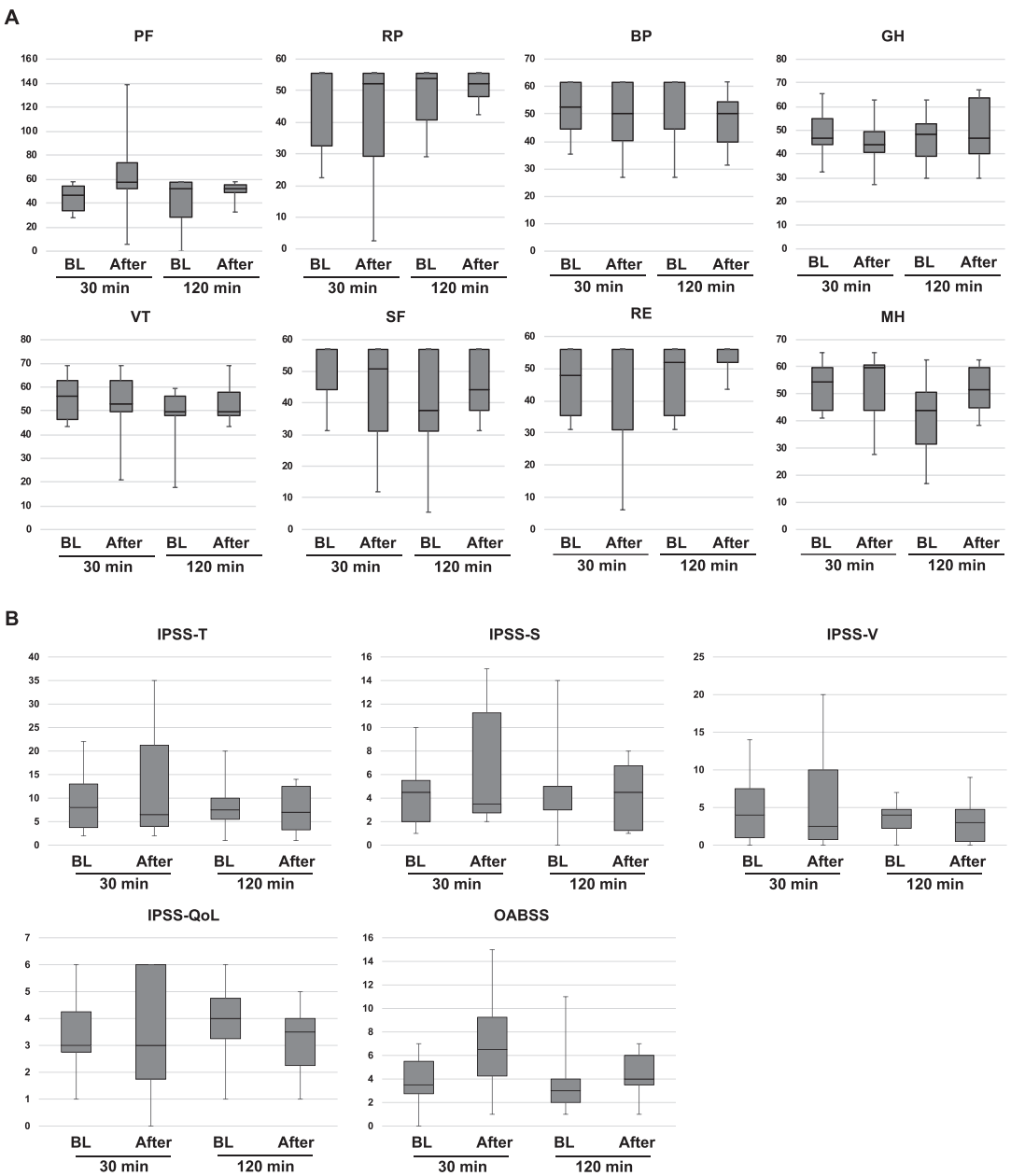
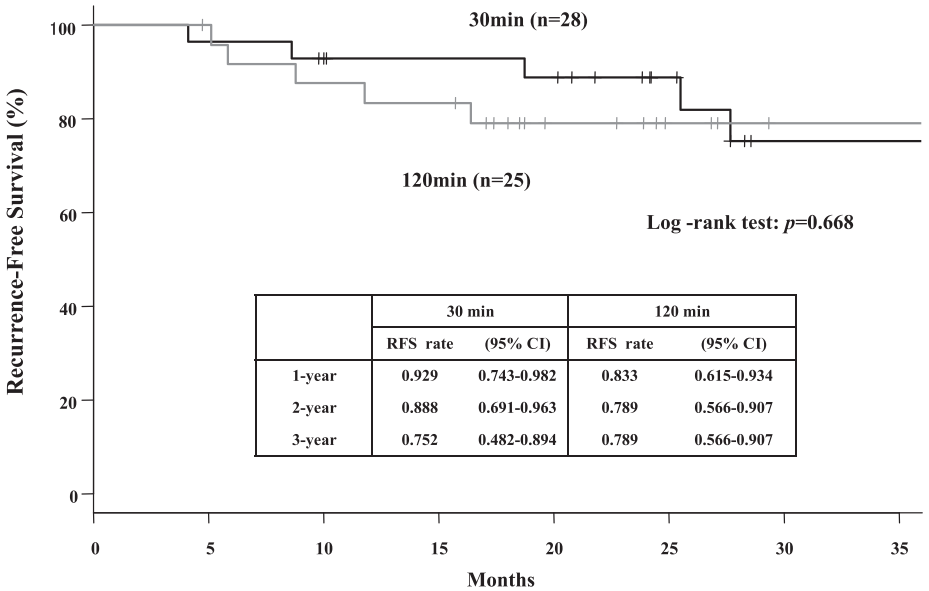


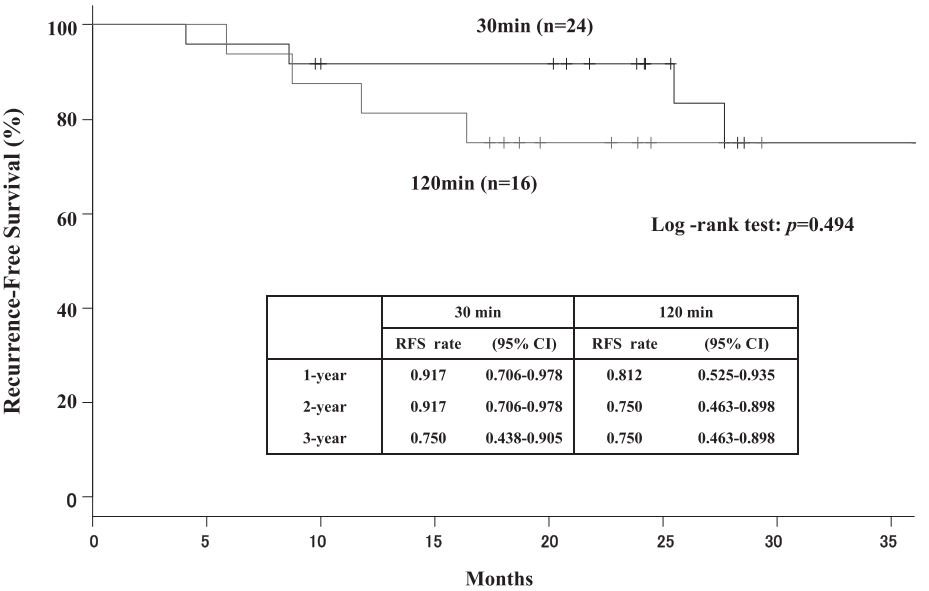
Fig. 2 HRQoL and lower urinary tract symptoms.
A. Scores of SF-36 domains. The medians and interquartile ranges are shown. PF: Physical Functioning, RF: Role Physical, BP: Bodily Pain, GH: General Health Perceptions, VT: Vitality, SF: Social Functioning, RE: Role-Emotional and MH: Mental Health.
B. Scores of lower urinary tract symptoms. The medians and interquartile ranges are shown. BL: Baseline, After: after the protocol treatment.

90.7) at 2 years, and 75.2% (95% CI: 48.2–89.4) vs. 78.9% (same as at 2 years because no events had occurred since then) at 3 years. Kaplan–Meier analysis revealed no significant difference in recurrence-free survival between those arms (Log-rank test: p=0.668) (**Fig. 3**). Hazard ratio for recurrence-free progression was 0.76 (95% CI: 0.22–2.63). Regarding PPS, similar to FAS, no significant difference in recurrence-free survival was observed between those two arms by Kaplan–Meier analysis (**Fig. 4**).



	30 min		120 min	
	RFS rate	(95% CI)	RFS rate	(95% CI)
1-year	0.929	0.743-0.982	0.833	0.615-0.934
2-year	0.888	0.691-0.963	0.789	0.566-0.907
3-year	0.752	0.482-0.894	0.789	0.566-0.907

Fig. 3 Kaplan–Meier estimate of recurrence-free survivals (RFS) between the 30-min arm and the 120-min arm. The inset shows the RFS rate and 95% CI at 1, 2 and 3 years.



	30 min		120 min	
	RFS rate	(95% CI)	RFS rate	(95% CI)
1-year	0.917	0.706-0.978	0.812	0.525-0.935
2-year	0.917	0.706-0.978	0.750	0.463-0.898
3-year	0.750	0.438-0.905	0.750	0.463-0.898

Fig. 4 Kaplan–Meier estimate of recurrence-free survivals (RFS) between the 30-min arm and the 120-min arm in PPS. The inset shows the RFS rate and 95% CI at 1, 2 and 3 years.

Safety

Treatment-emergent adverse events are summarized in **Table 3**. The most common AEs in either of the groups were urinary tract pain, urinary frequency and hematuria. It appears paradoxical that more patients with the shorter THP intravesical dwell time experienced urinary frequency and hematuria. However, among the patients who experienced urinary frequency, 9 patients in the 30-min group and only 1 patient in the 120-min group could continue the protocol treatment by the conservative approach, and the remaining patients (4 in the 30-min group and 5 in the 120-min group) had to discontinue the treatment due to accompanying urinary tract pain. Regarding hematuria, all cases were Grade 1 and accompanied with urinary tract pain or urinary frequency. Among those, 2 patients in the 30-min group and 1 patient in the 120-min group discontinued the protocol treatment due to accompanying urinary tract pain. Grade 3 urinary tract pain was observed in 2 patients (8.0%) of the 120-min group, and in one of those it was accompanied with Grade 3 prostate infection. No Grade 3 AEs occurred in the 30-min group. Grade 4 or 5 AEs did not occur in either of the two groups.

Table 3 Adverse events.

Events	30 mins (N=28)		120 mins (N=25)	
	All Grades	Grade 3	All Grades	Grade 3
	Number of patients (percent)			
Any adverse event	17 (60.7)	0 (0.0)	17 (68.0)	2 (8.0)
Urinary tract pain	16 (57.1)	0 (0.0)	17 (68.0)	1 (4.0)
Urinary frequency	13 (46.4)	0 (0.0)	6 (24.0)	0 (0.0)
Hematuria	4 (14.3)	0 (0.0)	1 (4.0)	0 (0.0)
Urinary incontinence	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary retention	2 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
Prostate infection	0 (0.0)	0 (0.0)	1 (4.0)	1 (4.0)
Hypotension	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)

Discussion

In this study, we analyzed the health-related quality of life, efficacy and adverse events following two different dwell times of THP intravesical chemotherapy as single immediate and additional adjuvant therapy for prevention of recurrence in IR NMIBC patients. After randomization and TURBT, 36.5% (23 out of 63) in the 30-min group and 39.7% (25 out of 63) in the 120-min group were excluded from the study because the pathology results did not satisfy the study criteria. Among them, 8 patients in the 30-min group and 12 patients in the 120-min group had concomitant CIS. All of them were actually classified into intermediate-risk group according to the EORTC scoring system when other factors, such as T stage, grade, tumor size and number of tumors, were taken into consideration (data not shown), and all CIS lesions were identified from random biopsies of bladder mucosa with normal appearance. This means that CIS was present in 21.1% (8 out of 38) and 29.3 % (12 out of 41) of patients with intermediate-risk in the 30-min and 120-min groups, respectively. These incident rates are concordant with the report by Hara *et al*., in which they showed that 24.7% of IR NMIBC cases had CIS in normal-looking sites[15].

We could not observe any statistical difference in changes of the measurement of HRQoL and lower urinary tract symptoms by the protocol treatment between the two study arms. Since only a limited number of patients were available for this analysis, it is difficult to conclude that there was no difference in HRQoL and lower urinary tract symptoms between the two different dwell times for THP intravesical chemotherapy. We were able to collect the questionnaire book from only 12 patients (50%) and 10 patients (63%) from the 30-min and 120-min groups, respectively, because the remaining patients had lost the questionnaire book during the protocol treatment. This may have hampered the sufficient study power. Another possible explanation is that the patients who could complete the protocol treatment were not significantly suffering and therefore their HRQoL was not compromised.

Recurrence-free survival was not significantly different between the two study arms. This suggests that 30 min might be sufficient for THP to exert its efficacy on the prevention of recurrence following resection of IR NMIBC in both single immediate and additional adjuvant chemotherapy. One of the characteristics of THP is its rapid penetration to tissue. Akaza *et al.* showed that THP needs a shorter dwell time than ADM to exert its anti-tumor effect on bladder tumors using an *in vitro* model[9]. Nakagawa *et al*. showed even 5-min dwell exhibited an anti-tumor effect[10]. Sugano *et al*. showed in their non-blinded non-randomized trial that repetitive 30-min dwell enabled sufficient THP penetration into bladder mucosa, and

concluded that 30 min is optimal as a THP dwell time compared to 10 min and 60 min in terms of both efficacy and adverse events[11]. However, it was not clear if 30-min dwell is sufficient for the purpose of single immediate or adjuvant therapy following TURBT because THP dwell time varies among the published randomized controlled studies.[16)-19)]. This is the first prospective study comparing two different THP retention times and it suggested that a difference in dwell time did not impact on preventing recurrence after TURBT of IR NMIBC. It is of note that recurrence-free rates in either of the study arms in this study are also comparable to or even better than those of previous studies which employed 60-min to 120-min dwell time for additional adjuvant THP intravesical chemotherapy[16) 17) 19)].

Despite its lower frequency of AE compared to BCG, controlling urinary tract pain seems to be a key issue for NMIBC patients to complete the entire treatment during the adjuvant intravesical instillation of THP after TURBT. Although we could not observe any significant difference in HRQoL and lower urinary symptom measurements between the two study arms, we observed more frequent self-reporting of adverse events in the 120-min arm. In addition, more patients in the 120-min arm could not complete the protocol treatment due to urinary tract pain, which was the most frequently observed AE in this study. Furthermore, 2 patients in the 120-min arm experienced Grade 3 AEs. Since 30-min dwell does not seem to compromise the prophylactic effect on IR NMIBC, this duration might be an optimal option in terms of both efficacy and safety.

There are limitations in the present study. First, since there had been no evidence of either safety or the recurrence-free survival of IR NMIBC using the protocol treatment in this study and since a non-inferiority trial design was not feasible, we had to employ a randomized phase II selection design for this study, which requires subsequent confirmatory studies. Second, the criteria for excluding inappropriate subjects from the FAS population, such as those with incomplete records due to being lost to follow-up and those with protocol violation, were not described in the original protocol. Third, we had incomplete patient recruitment and a high dropout rate before initiation of the protocol treatment. This suggests the possibility of insufficient study power. Fourth, we were able to collect analyzable SF-36 data only from patients who completed the protocol treatment, which compromised the strength of this study. Fifth, the participants were only Japanese therefore external validations with other racial backgrounds and lifestyles are needed.

Conclusions

This study did not show any difference in either HRQoL or efficacy with regard to NMIBC recurrence between 30-min and 120-min dwell for THP intravesical chemotherapy. However, it was suggested that the former may reduce the risk of adverse events. Although the optimal frequency and dwell time of additional adjuvant intravesical chemotherapy after single immediate instillation still remain unknown[20)] and further large randomized-control trials are warranted to address this issue, this study provides useful information for future study design.

Conflicts of interest

Yoshiaki Kawano is currently an employee of GlaxoSmithKline and owns stocks/shares in GlaxoSmithKline. All remaining authors have declared no conflicts of interest. There were no external sources of funding for this study.

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筋層非浸潤性膀胱癌に対するピラルビシンの TURBT 後即時単回膀胱注入療法および維持療法における保持時間の検討

―― 多施設共同無作為化比較試験 ――

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抄録：

【はじめに】中リスク筋層非浸潤性膀胱癌（IR NMIBC）において，抗癌剤の術後即時膀胱注入に加え維持療法を行うことは，再発率の低下に繋がるとされている。一方で，継続的な膀胱内への抗癌剤注入は，膀胱刺激症状を惹起したり，その処置自体への抵抗から患者の QOL を損なうこともある。本研究では，維持膀注時のピラルビシン（THP）の膀胱内滞留時間に着目し，SF-36 を用いた健康に関する QOL（HRQOL）と有効性の観点から 2 つの注入時間（30 分，120 分）を比較した。

【対象と方法】TURBT 術前に 126 名の患者を無作為に THP30 分群と THP120 分群に割り付け，術後の病理結果から IR NMIBC と診断された患者 59 名に protocol 通りの維持膀注療法を行った。

【結果】最も一般的な有害事象は，尿路痛（57.1％対 68.0％），頻尿（46.4％対 24.0％），および血尿（14.3％対 4.0％）であった。傾向として 120 分群で尿路痛による維持膀注の中止が多くみられたが，SF-36 ドメイン，IPSS および OABSS のスコアの変化と無再発生存率は，2 つの群間で有意差を認めなかった。120 分群では Grade 3 の尿路痛と前立腺炎が 1 名ずつ認められた。

【おわりに】IR NMIBC に対する THP 維持膀注では薬剤の膀胱内滞留時間を 30 分にすることで，120 分に劣らない有効性を担保しつつ有害事象のリスクを減らす可能性が示唆された。 （西日泌尿．**82**：497-507, 2020）

キーワード：中リスク筋層非浸潤性膀胱癌，ピラルビシン，膀胱内注入療法